CLAIM LISTING

1. (Currently amended) A method of:

a) inhibiting the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters; and/or

b) modulating the plasma level of free fatty acids, glycerol, LDL-cholesterol, HDL-cholesterol, insulin and/or glucose; and/or

c) modulating intracellular triacylglycerol and cholesterol ester stores, intracellular level of fatty acids, fatty acid esters, ~~such as~~ diacylglycerols, phosphatidic acids, long chain acyl-CoA's as well as citrate or malonyl-CoA; and/or

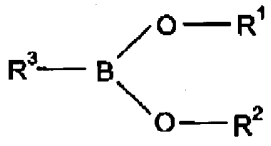
d) increasing insulin sensitivity in adipose tissue, skeletal muscle, liver or pancreatic β cells; and/or

e) modulating insulin secretion from pancreatic β cells; and/or

f) inhibiting male fertility

in a patient comprising, administering to a patient in need of such ~~treatment~~ **method** a therapeutically effective amount of a boronic acid, an ester thereof, a prodrug thereof,

wherein the boronic acid, an ester thereof or a prodrug thereof is of the general formula I



(I)

wherein R^1 and R^2 are independently selected from hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro,

silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl;

wherein R^2 is optionally covalently bound to R^1 by one or two ether, thioether, O-B, C-C, C=C or C-N bonds, to form a ring system with the O-atoms to which R^1 and R^2 are bound; and

R^3 is selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, thioxo, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-

alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl;

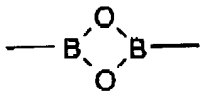
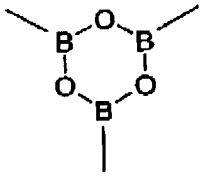
or any tautomeric forms, stereoisomers, mixture of stereoisomers, racemic mixture, oligomers or polymorphs,

or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof.

2. (Currently amended) The method according to claim 1, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 2.0 and 11.5 ~~, between 3.0 and 10.5, between 4.0 and 9.5, between 5.0 and 8.5, preferably between 5.5 to 8.0, and most preferable between 6.0 to 7.5~~.

3. (Original) The method according to claim 1, wherein the boronic acid, an ester thereof or a prodrug thereof is a dimer or trimer of a boronic acid.

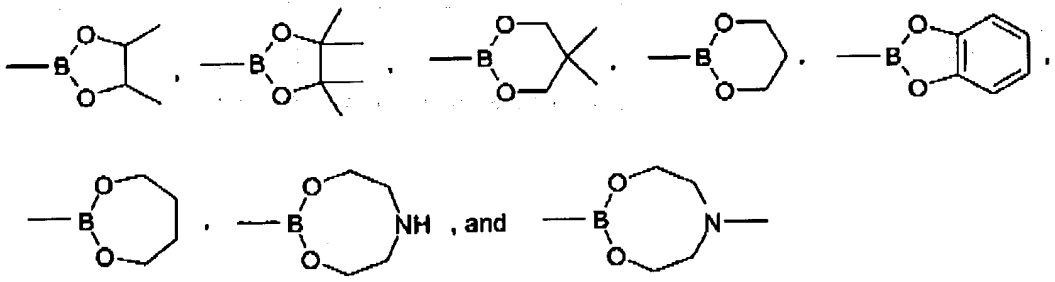
4. (Original) The method according to claim 3, wherein said dimer or trimer of the boronic acid comprises a structure selected from:


and


5. (Original) The method according to claim 1, wherein the boronic acid, an ester thereof or a prodrug thereof comprises an atom selected from the group consisting of S, P, I, Br, Si, Se and Ge.

6. Cancelled)

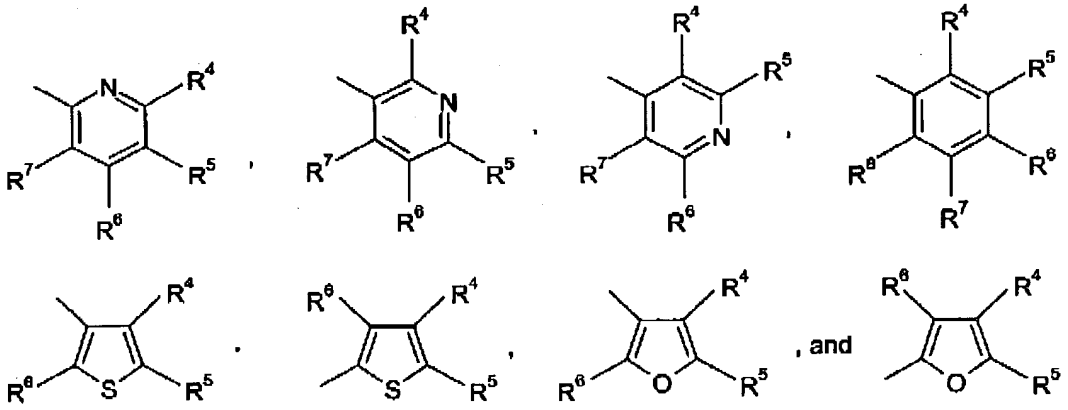
7. (Currently amended) The ~~use~~ **method** according to claim 1, wherein the boronic acid, an ester thereof, or a prodrug thereof, comprises a structure selected from the group consisting of



8. (Currently amended) The ~~use~~ **method** according to claim ~~6~~ **1**, wherein the group R^3 in the general formula (I) comprises an optionally substituted moiety selected from the group consisting of pyrrolidine-2-yl, pyrrolidine-3-yl, pyrrole-2-yl, pyrrole-3-yl, 3H-pyrrole-2-yl, 3H-pyrrole-3-yl, 3H-pyrrole-4-yl, 3H-pyrrole-5-yl, oxolane-2-yl, oxolane-3-yl, furane-2-yl, furane-3-yl, thiolane-2-yl, thiolane-3-yl, thiophene-2-yl, thiophene-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, pyrazolidine-3-yl, pyrazolidine-4-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, imidazolidine-2-yl, imidazolidine-4-yl, 3H-pyrazole-3-yl, 3H-pyrazole-

4-yl, 3H-pyrazole-5-yl, isoxazole-3-yl, isoxazole-4-yl, isoxazole-5-yl, oxazole-2-yl, oxazole-4-yl, oxazole-5-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, 1,2,5-oxadiazole-3-yl, 1,3,5-oxadiazole-2-yl, 1,3,5-oxadiazole-4-yl, 1,3,4-oxadiazole-2-yl, 1,2,3,5-oxatriazole-4-yl, 1,2,5-thiadiazole-3-yl, 1,3,5-thiadiazole-2-yl, 1,3,5-thiadiazole-4-yl, 1,3,4-thiadiazole-2-yl, 1,2,3,5-thiatriazole-4-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, 1,2,5-triazole-3-yl, tetrazole-5-yl, 1,3-oxathiole-2-yl, 1,3-oxathiole-4-yl, 1,3-oxathiole-5-yl, benzofurane-2-yl, benzofurane-3-yl, isobenzofurane-1-yl, benzothiophene-2-yl, benzothiophene-3-yl, isobenzothiophene-1-yl, 1H-indole-2-yl, 1H-indole-3-yl, 2H-isoindole-1-yl, indolizine-1-yl, indolizine-2-yl, indolizine-3-yl, 1H-benzimidazole-2-yl, 1H-benzothiazole-2-yl, 1H-benzoxazole-2-yl, 1H-benzisooxazole-3-yl, 3H-indazole-3-yl, piperedine-1-yl, piperedine-2-yl, piperedine-3-yl, piperedine-4-yl, piperazine-1-yl, piperazine-2-yl, 2,5-dione-piparazine-1-yl, 2,5-dione-piparazine-3-yl and phenyl.

9. (Currently amended) The method according to claim ~~6~~ 1, wherein the group R^3 is selected from the group consisting of:



wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, ~~oxo,~~ thioxo, ~~halogen,~~ amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-

alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl, wherein each of hydroxy, sulfanyl, sulfonyl, sulfinyl, amino, imino, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, sulfanyl, sulfonyl, sulfinyl, oxo, thioxo, halogen, amino, imino, cyano, nitro, silyl, boranyl, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-heterocyclyl and C_{3-10}-cycloalkyl.

10. (Currently amended) The method according to claim 9, wherein the molar weight of each of R^4, R^5, R^6, R^7 and R^8 ~~are~~ is below about 100 Dalton~~, preferably below about 80 Dalton, more preferable below 50 Dalton and even more preferable below about 20 Dalton~~.

11. (Original) The method according to claim 9, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, hydroxyl, perhalomethyl, perhalomethoxy, C_{1-6}-alkyl, C_{1-6}-alkoxy and C_{1-6}-alkylthio.

12. (Original) The method according to claim 9, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, methyl, methoxy, thiomethoxy, perhalomethyl, perhalomethoxy

13. (Original) The method according to claim 9, wherein R^4, R^5, R^6, R^7 and R^8 are independently selected from hydrogen, halogen, trifluoromethyl and trifluoromethoxy.

14. (Currently amended) The method according to claim ~~6~~ 1, wherein the group R^1 is H.

15. (Currently amended) The method according to claim ~~6~~ 1, wherein the group R^1 is H and the group R^2 is H.

16. (Currently amended) The method according to claim 1, wherein said boronic acid, an ester thereof or a prodrug thereof is selected from the group consisting of:
2-(5-Chlorothiophen-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(5-Chlorothiophen-2-yl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5-Chlorothiophen-2-yl)-[1,3,6,2]dioxazaborocane,
2-(3,5-Difluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Bromophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chlorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Fluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Trifluoromethylphenyl)-[1,3,6,2]dioxazaborocane,
2-(3,4,5-Trifluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborinane,
2-(5-Chloro-2-methoxyphenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Trifluoromethoxyphenyl)-[1,3,6,2]dioxazaborocane,
2-(3,5-Dichlorophenyl)-[1,3,6,2]dioxazaborocane,
2-(3-Chloro-4-fluorophenyl)-[1,3,6,2]dioxazaborocane,
2-(4-Methylthiophen-2-yl)-[1,3,6,2]dioxazaborocane,
2-(3-Bromophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(5-Chloro-2-methoxyphenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3,4,5-trifluorophenyl)-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborinane,
2-(3,5-Dichlorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
2-(3-Fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
5,5-Dimethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborinane,
2-(3-Bromophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(5-Chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborolane,

2-(3,5-Dichlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(3-Chloro-4-fluorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
2-(3-Chlorophenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(3-trifluoromethylphenyl)-[1,3,2]dioxaborolane,
4,4,5,5-Tetramethyl-2-(4-methylthiophen-2-yl)-[1,3,2]dioxaborolane,
4-Benzyloxyphenylboronic acid,
4-Bromobenzeneboronic acid n-methyldiethanolamine cyclic ester,
2-(3,5-Difluorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane,3-Bromobenzeneboronic acid n-methyldiethanolamine cyclic ester,
2-(4-Bromophenyl)-5,5-dimethyl-1,3,2-dioxaborinane,
2-(2-Chlorophenyl)-5,5-dimethyl-1,3,2-dioxaborinane,
2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzonitrile,
2-(2-Fluoro-phenyl)-5,5-dimethyl-[1,3,2]dioxaborinane,
~~2-(5,5-Dimethyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid ethyl ester,~~
5-Chloro-2-methoxyphenylboronic acid,
3,5-Dibromophenylboronic acid,
3-Ethoxyphenylboronic acid,
3-phenylphenylboronic acid,
4-fluorophenylboronic acid,
2-Bromophenylboronic acid,
3-Bromophenylboronic acid,
2,6-Dichlorophenylboronic acid,
3-Methylphenylboronic acid,
2-Chlorophenylboronic acid,
3-Chlorophenylboronic acid,
3-(Trifluoromethoxy)benzeneboronic acid,
3-Trifluoromethylphenylboronic acid,
3,5-Bis(Trifluoromethyl)phenylboronic acid,
3,5-Dichlorophenylboronic acid,
3-Chloro-4-fluorophenylboronic acid,
3,5-Difluorophenylboronic acid,
3-Fluorophenylboronic acid,
2,3-Difluoro-4-pentylphenylboronic acid,
(3-Dluoro-4-benzyloxyphenyl)boronic acid,
3,4,5-Trifluorophenylboronic acid,
2,3,5-Trichlorophenylboronic acid,
2,5-Dichlorophenylboronic acid,
2,3-Difluorophenylboronic acid,
2,5-Difluorophenylboronic acid,
4'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)acetanilide,
3,4-Difluorophenylboronic acid,
2,3-Dichlorophenylboronic acid,
2,3-Difluoro-4-bromophenylboronic acid,
3-Fluoro-4-phenylboronic acid,
2-Methoxy5-fluorophenylboronic acid,
3,4-Dichlorophenylboronic acid,
5-Indolyl boronic acid,

3-Formylphenylboronic acid,
~~4-(N,N-dimethylcarbamoyl)phenylboronic acid,~~
6-Methoxy-2-phenyl-hexahydro-pyrano[3,2-a][1,3,2]dioxaborinine-7,8-diol,
~~2-Fluoro-4-(5-pentyl-[1,3,2]dioxaborinan-2-yl)-benzoic acid,~~
~~4-(3-Iodo-phenoxymethyl)-2-phenyl-[1,3,2]dioxaborolane,~~
3'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-trimethylsilylthiophen,
4'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)2-nitrothiophene,
1-Benzothiophen-3-ylboronic acid,
2-Formyl-3-thiopheneboronic acid,
2-Thien-3-yl-1,3,2-benzodioxaborole,
3-Thiophenboronic acid,
2-(2-Formyl-3-methylthien-5-yl)-1,3,2-dioxaborinane,
4-Methylthiophene-2-boronic acid,
5-Methylfuran-2-boronic acid,
5-Methylthiophene-2-boronic acid,
~~Benzo[b]furan-2-boronic acid,Benzo[B]thiophene-2-boronic acid,Furan-2-boronic acid,5-Chlorothiophene-2-boronic acid,5-Cyanothiophene-2-boronic acid,5-Acetylthiophene-2-boronic acid,Thiophene-2-boronic acid,3-Bromothiophene-2-boronic acid, and5,5-Dimethyl-2-(3-iodothiophen-2-yl)-[1,3,2]dioxaborinane~~
Benzo[b]furan-2-boronic acid,
Benzo[B]thiophene-2-boronic acid,
Furan-2-boronic acid,
5-Chlorothiophene-2-boronic acid,
5-Cyanothiophene-2-boronic acid,
5-Acetylthiophene-2-boronic acid,
Thiophene-2-boronic acid,
3-Bromothiophene-2-boronic acid, and
5,5-Dimethyl-2-(3-iodothiophen-2-yl)-[1,3,2]dioxaborinane.

17. (Currently amended) The method according to claim 6, wherein ~~R^3 is characterized in pK_a of~~ the compound **is** R^3-$B(OH)_2$ **and the pK_a of the R^3** substituent is ~~being~~ between 2.0 and 11.5~~, between 3.0 and 10.5, between 4.0 and 9.5, between 5.0 and 8.5, preferably between 5.5 to 8.0, and most preferable between 6.0 to 7.5~~.

18. (Original) The method according to claim 1, wherein said boronic acid, or an ester thereof or a prodrug thereof has a molar weight of no greater than 1000 D.

19. (Currently amended) The method according to claim 1, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 750 D ~~, preferably less than 500 D, more preferable less than 350 D, more preferable less than 300 D, more preferable less than 250 D and even more preferable less than 200 D~~.

20. (Currently amended) The method according to claim 1, wherein said boronic acid, an ester thereof or a prodrug thereof has an IC_{50} value as determined by the assay 3190.2 or 3180.1 disclosed herein of less than 50 μM ~~, preferably less than 5 μM, more preferable less than 500 nM and even more preferable less than 100 nM~~.

21. (Currently amended) The method according to claim 1, wherein said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2.0 of at least 0.5 mg/L ~~, preferably at least 2.5 mg/L, more preferable at least 20 mg/L, even more preferable at least 200 mg/L and most preferable at least 2 g/L~~.

22. (Original) The method according to claim 1, wherein administration of said boronic acid, an ester thereof or a prodrug thereof is by the oral, nasal, transdermal, pulmonal, or parenteral route.

23. (Currently amended) The method according to claim 1, wherein a pharmaceutical composition is administered, said pharmaceutical composition comprising, as an active ingredient, ~~a~~ **said** boronic acid, ~~an~~ **said** ester thereof, ~~a~~ **said** prodrug thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, together with a pharmaceutically acceptable carrier or diluent.

24. (Currently amended) The method according to claim 2, wherein a pharmaceutical composition is administered, said pharmaceutical composition comprising, as an active ingredient, ~~a~~ **said** boronic acid, ~~an~~ **said** ester thereof or ~~a~~ **said** prodrug thereof, or a

pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

25. (Currently amended) The ~~pharmaceutical composition~~ **method** according to claim 24 **wherein the pharmaceutical composition** in unit dosage form, comprising from about 0.05 mg to about 2000 mg, preferably from about 0.1 to about 500 mg of the boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof.

26. (Currently amended) The ~~pharmaceutical composition~~ **method** according to claim 23 **wherein the pharmaceutical composition is** for oral, nasal, transdermal, pulmonal or parenteral administration.

27. (Original) A method according to claim 1 for treating a disorder where it is desirable to inhibit the lipolytic activity of hormone-sensitive lipase against triacylglycerols, diacylglycerols, cholesterol acyl esters or steroid acyl esters.

28. (Original) A method according to claim 1 for treating a disorder where it is desirable to modulate the plasma level of free fatty acids or to modulate the handling, storage and oxidation of intracellular fatty acid and cholesterol.

29. (Original) The method according to claim 27, wherein said disorder is selected from the group consisting of insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof.

30. (Original) The method according to claim 28, wherein said disorder is selected from the group consisting of insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, obesity, abnormalities of lipoprotein metabolism and any combination thereof.

31. (Currently amended) A method of treating ~~a patient suffering from~~ insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, hyperlipoproteinemia, hypertriglyceridemia, hyperlipidemia, hypercholesterolemia, or other abnormalities of lipoprotein metabolism, said method comprising administering to ~~the patient~~ **a patient in need thereof** a pharmaceutically effective amount of a boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof.

32. (Currently amended) The method according to claim 31, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 2.0 and 11.5~~, between 3.0 and 10.5, between 4.0 and 9.5, between 5.0 and 8.5, preferably between 5.5 to 8.0, and most preferable between 6.0 to 7.5~~.

33. (Original) The method according to claim 27, wherein the patient is treated with said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for at least about 1 week, for at least about 2 weeks, for at least about 4 weeks, for at least about 2 months or for at least about 4 months.

34. (Original) The method according to claim 28, wherein the patient is treated with said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for at least about 1 week, for at least about 2 weeks, for at least about 4 weeks, for at least about 2 months or for at least about 4 months.

35. (Original) The method according to claim 31, wherein the patient is treated with said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof for at least about 1 week, for at least about 2 weeks, for at least about 4 weeks, for at least about 2 months or for at least about 4 months.

36. (New) The method according to claim 2, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 3.0 and 10.5.

37. (New) The method according to claim 2, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 4.0 and 9.5.

38. (New) The method according to claim 2, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 5.0 and 8.5.

39. (New) The method according to claim 2, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 5.5 to 8.0.

40. (New) The method according to claim 2, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 6.0 to 7.5.

41. (New) The method according to claim 10, wherein the molar weight of each of R^4, R^5, R^6, R^7 and R^8 is below about 80 Dalton.

42. (New) The method according to claim 10, wherein the molar weight of each of R^4, R^5, R^6, R^7 and R^8 is below 50 Dalton.

43. (New) The method according to claim 10, wherein the molar weight of each of R^4, R^5, R^6, R^7 and R^8 is below about 20 Dalton.

44. (New) The method according to claim 17, wherein the compound is R^3-$B(OH)_2$ and the pK_a of the R^3 substituent is between 3.0 and 10.5.

45. (New) The method according to claim 17, wherein the compound is R^3-$B(OH)_2$ and the pK_a of the R^3 substituent is between 4.0 and 9.5.

46. (New) The method according to claim 17, wherein the compound is R^3-$B(OH)_2$ and the pK_a of the R^3 substituent is between 5.0 and 8.5.

47. (New) The method according to claim 17, wherein the compound is R^3-$B(OH)_2$ and the pK_a of the R^3 substituent is between 5.5 to 8.0.

48. (New) The method according to claim 17, wherein the compound is R^3-$B(OH)_2$ and the pK_a of the R^3 substituent is between 6.0 to 7.5.

49. (New) The method according to claim 19, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 500 D.

50. (New) The method according to claim 19, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 350 D.

51. (New) The method according to claim 19, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 300 D.

52. (New) The method according to claim 19, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 250 D.

53. (New) The method according to claim 19, wherein the molar weight of said boronic acid, an ester thereof or a prodrug thereof is less than 200 D.

54. (New) The method according to claim 20, wherein said boronic acid, an ester thereof or a prodrug thereof has an IC_{50} value as determined by the assay 3190.2 or 3180.1 disclosed herein of less than 5 μM.

55. (New) The method according to claim 20, wherein said boronic acid, an ester thereof or a prodrug thereof has an IC_{50} value as determined by the assay 3190.2 or 3180.1 disclosed herein of less 500 nM.

56. (New) The method according to claim 20, wherein said boronic acid, an ester thereof or a prodrug thereof has an IC_{50} value as determined by the assay 3190.2 or 3180.1 disclosed herein of less than 100 nM.

57. (New) The method according to claim 21, wherein said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2.0 of at least 2.5 mg/L.

58. (New) The method according to claim 21, wherein said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2.0 of at least 20 mg/L.

59. (New) The method according to claim 21, wherein said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2.0 of at least 200 mg/L.

60. (New) The method according to claim 21, wherein said boronic acid, an ester thereof or a prodrug thereof has a solubility in water at 25 °C and pH 2.0 of at least 2 g/L.

61. (New) The method according to claim 25 wherein the pharmaceutical composition in unit dosage form, comprising from about 0.1 to about 500 mg of the boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable solvate thereof.

62. (New) The method according to claim 32, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 3.0 and 10.5.

63. (New) The method according to claim 32, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 4.0 and 9.5.

64. (New) The method according to claim 32, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 5.0 and 8.5.

65. (New) The method according to claim 32, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 5.5 to 8.0.

66. (New) The method according to claim 32, wherein the pK_a of said boronic acid, an ester thereof, a prodrug thereof or a pharmaceutically acceptable salt thereof is between 6.0 to 7.5.

RESPONSE

The examiner states in the Office Action Summary that claims numbered 1-35 are pending in the application; claims numbered 1-35 are rejected; and claims numbered 7, 8, 16, and 23-26 are objected to.

(1) The examiner objected to claims numbered 7, 8, 16, and 23-26 for various informalities noted on page 2 of the Office Action details. Applicant has amended claims numbered 7, 8, 16, and 23-26 as recommended.

Applicant respectfully requests reconsideration and withdrawal of the objections to claims numbered 7, 8, 16, and 23-26.

(2) The examiner has rejected claims numbered 31-35 under U.S.C. §112, first paragraph, as being indefinite, because the specification, while being enabling for a method of treating insulin resistance, diabetes type 1, diabetes type 2, metabolic syndrome X, impaired glucose tolerance, hyperglycemia, dyslipidemia, hyperlipoproteinemia, hypertriglyceridemia, hyperlipidemia, hypercholesterolemia, or other abnormalities of lipoprotein metabolism in patient in need thereof, does not reasonably provide enablement for a method of treating, in general, a patient who suffers from the above mentioned diseases/disorders.

Applicant has amended claim numbered 31 to more clearly define the invention.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

(3) The examiner has rejected claims numbered 1-30 and 32-35 under U.S.C. §112, second paragraph, as being indefinite f or failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the examiner states:

(a) Regarding claim 1 (line 6) [and thus its dependents], the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention.

(b) Claim 17 is not clear as to the manner in which it further limits the previous claim. It is believed that if it were amended to recite, in part, "wherein the compound is R^3-$B(OH)_2$ and the pKa of the R^3 substituent is...".

(c) Claims 2, 10, 17, 19-21, 25 and 32 contain a broad range together with a narrow range that falls within the broad range, e.g., in claim 2 a broad range of pKa values of between 2.0 and 11.5 is set forth and is then followed by several other ranges which are narrower in scope.

Applicant has amended claims numbered 1, 2, 10, 17, 19, 20, 21 and 32, and added new claims numbered 36-66, to more clearly define the invention.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

(4) The examiner has rejected claims numbered 1, 2, 6, 9, 10, 14, 15, 17-32 under 35 U.S.C. §102(a) as being anticipated by Holmes-Farley et al. (U.S. Patent Application Publication No. 2003/0064963) who teach methods of treating obesity, Type II diabetes mellitus, impaired glucose tolerance, lipid syndromes, hyperglycemia, hypertriglyceridemia, and hyperlipidemia (page 4, cols. 1-2, section [0046] which comprises administering from about 5 mg/day to about 10 grams/day (page 4, col. 2, section [0048] by a route that may be oral, rectal, nasal, pulmonary or topical (page 4, col. I, section [0045] of a pharmaceutical composition which may comprise an acceptable pharmaceutical carrier page 4, col. 2, section [0047] and boronic acid compounds, including esters and salts, encompassed by the present claims (see the first row of chemical compounds depicted in Figure 4A, 4D, 4E; col. 1, sections [0005]-[0010]; page 2, col. 1, section [0022]; page 2, col. 2, section [0027]; page 4, col. 1, section [0043]; and page 4, col. 2, section [00501). The examiner suggests applicant compare the structures of Holmes-Farley et al. with the definition provided in present claim 6 and in claim 9 there the R^3 substituent may be a phenyl substituted with a C1-6 alkyl which in turn my be substituted with an oxo and a halo group.

Applicant has amended claim 1 to incorporate the limitations of claim 6, and removed oxo and halogen as substituents from the second "wherein clause" of the original claim 6, found on page 53, line 21 of the specification as originally filed. Applicant has also amended claim number 9 to remove the oxo and halogen substituents. Applicant believes these amendments obviate the examiner's rejections.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a).

(5) The examiner has rejected claims numbered 1, 2, 18, 19 and 2 1-32 under 35 U.S.C. 102(a) as being anticipated by Henderson et al. (U.S. Patent Application Publication No. 2002/012832) who teaches the treatment of diabetic retinopathy (page 1, col. 2, section [0008]) which comprises administering from between about 0.001 to 500 mg (page 8, col. 2, section [0144] by a route that may be oral, rectal, percutaneous or parenteral (page 7, col. 2, section [0139] of a pharmaceutical composition which may comprise an acceptable pharmaceutical carrier (page 7, col. 2, section [0139] and boronic acid compounds, including salts thereof (page 2, col. 2, section [0031] and page 6, col. 2, section [0106].

The patients of the prior art suffer from diabetic retinopathy and therefore diabetes and thus are the patient population of the present claims. The biochemical processes of claim 1 are deemed to be inherent in the prior art compound because such compound is administered to the same host. Also, because of the close structural similarity between the prior art compound and those of the present invention where R^3 may be a substituted heteroaryl moiety (see present claim 6, for example), it is believed that that the physical constants as in present claims 2, 10, 18, 19, 21 and 32 would also be inherent.

Applicant has amended claim 1 to incorporate the limitations of claim 6, and removed oxo and halogen as substituents from the second "wherein clause" of the original claim 6, found on page 53, line 21 of the specification as originally filed. Applicant has also amended claim number 9 to remove the oxo and halogen substituents. Applicant believes these amendments obviate the examiner's rejections.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a).

(6) The examiner has rejected claims numbered 22, *25*, 26 and 33-35 under 35 U.S.C. 103(a) as being unpatentable over Holmes-Farley et al., as above.

The differences between the above and the claimed subject matter lie in that Holmes-

Farley et al. fail to teach:

(1) a parenteral route of administration; and

(2) the presently claimed duration of treatment and dosage range.

The examiner states however, to the skilled artisan, the claimed subject matter would have been obvious because:

(a) The reference teaches various routes of administration and thus the skilled artisan would have appreciated that the drugs could be introduced into the body through various routes. The artisan would have been motivated to employ a parenteral route of administration because it is an easy means of administration and was one that was well known to the skilled artisan. Also, the artisan would have also taken into consideration the patient's acceptance of any given route of administration; and

(b) The dosages taught by the reference are characterized as being only "typical" (page 4, col. 2, section [0048], line 6). The skilled artisan would have been motivated to vary the dosages, as well as the duration of treatment based upon the patient's individual characteristics such as general health, severity of disease, age, sex, body weight and tolerance to drugs.

Applicant has amended claim 1 to incorporate the limitations of claim 6, and removed oxo and halogen as substituents from the second "wherein clause" of the original claim 6, found on page 53, line 21 of the specification as originally filed. Applicant has also amended claim number 9 to remove the oxo and halogen substituents. Applicant believes these amendments obviate the examiner's rejections.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

(7) The examiner states claims numbered 22, 25, 26 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson, as above.

The differences between the above and the claimed subject matter lie in that Holmes-Farley et al. fail to teach:

(1) a nasal or pulmonary route of administration; and

(2) the presently claimed duration of treatment and dosage range.

The examiner states however, to the skilled artisan, the claimed subject matter would have been obvious because:

(a) The reference teaches various routes of administration and thus the skilled artisan would have appreciated that the drugs could be introduced into the body through various routes. The artisan would have been motivated to employ any of the known routes of administration in order to ensure proper compliance with the prescribed therapy and would have also taken into consideration the patient's acceptance of any given route of administration; and

(b) The dosages taught by the reference are characterized as being only "general" (page 8, col. 2, section [0144], line 1). The skilled artisan would have been motivated to vary the dosages, as well as the duration of treatment, based upon the patient's individual characteristics such as general health, severity of the disease, age, sex, body weight and tolerance to drugs.

Applicant has amended claim 1 to incorporate the limitations of claim 6, and removed oxo and halogen as substituents from the second "wherein clause" of the original claim 6, found on page 53, line 21 of the specification as originally filed. Applicant has also amended claim number 9 to remove the oxo and halogen substituents. Applicant believes these amendments obviate the examiner's rejections.

Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

Attorney Docket No. 6413.204-US
Ebdrup et al.
Serial No. 10/614,233 Filed July 7, 2003

The examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

Date: September 27, 2004

Rosemarie R. Wilk-Orescan
Registration Number 45,220
Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5969

Use the following customer number for all correspondence regarding this application.

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